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EXAMINER	
KIM, ALEXANDER D	
ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,159	PETERSEN ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-91 and 93-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-91 and 93-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *dipole Marriam Webster Online*.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 02/07/2008), Applicants filed a response and amendment received on 10/04/2008. Said amendment cancelled Claims 1-87 and 92; amended Claims 88-90; and added new Claims 93-112.

Claims 88-91 and 93-112 are pending in the instant Office action and will be examined herein.

Withdrawn-Objections to the Specification

2. The previous objection to the specification because the title is not descriptive of the claims is withdrawn by virtue of Applicants' amendment.

Withdrawn-Claim Objections

3. The previous objection of Claims 31-50 and 88-92 which were not written in order, wherein the order has independent claim first in claims, is withdrawn by virtue of Applicants' amendment.

4. The previous objection of Claims 40 and 42 disclose a symbol "Å" wherein the said abbreviation should be spelled out in the claim at the time of first appearance; is withdrawn by virtue of Applicants' amendment.

5. The previous objection of Claim 46 is withdrawn by virtue of cancelling Claim 46.

6. The previous objection of Claim 88 for reciting "whereon" is withdrawn by virtue of Applicants' amendment (i.e., amending it to "and").

7. The previous objection of Claim 88 for reciting "a coupling" at the end of step b); wherein it should be ---a coupling with the carrier---; is by virtue of Applicants' amendment.

8. The previous objection of Claim 88 for reciting "a coupling" at the end of step b) is withdrawn by virtue of Applicants' amendment.

9. The previous objection of Claim 88 for reciting "thiol group; or" at the end is withdrawn by virtue of Applicants' amendment.

Claim Objections

10. Claims 90 and 103 are objected to because of the following informalities:

(a) Claim 90 recites "1 micrometer of less". It should be ---1 micrometer or less---.

(b) Claim 103 recites "(His, Lys, Arg)(Asp, Glu)". It should be ---(His, Lys, Arg, Asp, Glu)---.

Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 112

11. The previous rejection of Claims 36 and 38 under of 35 U.S.C. 112, second paragraph, for reciting "about 295nm, 275 nm or 254 nm" or "about 295nm" (which are recited in newly added claims 97 and 99), is withdrawn by virtue of Applicants' amendment (i.e., one skilled in the art would understand the term "about" used in the context of the claims and specification means the wavelength plus or minus the standard error associated with such instrumentation, which also depends on sensitivity, See page 8, middle of Remarks filed on 10/4/2008).

12. The previous rejection of Claim 41 under of 35 U.S.C. 112, second paragraph, for reciting "the plane of the disulfide bridge" is withdrawn by virtue of cancelling claims.

13. The previous rejection of Claim 42 under of 35 U.S.C. 112, second paragraph, for reciting "over-represented" and "under-represented" is withdrawn by virtue of cancelling claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 102 and 103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 102 recites "the plane of the dipole" and "the plane of the absorbing dipole". The dipole is "a pair of equal and opposite electrical charges or magnetic poles of opposite sign separated especially by a small distance" according to Miriam-Webster OnLine dictionary (see the attachment). The plane supposed to be shape like a sheet of paper, for example, and it is unclear what is encompassed by the recitation of "the plane of the dipole". It is also unclear what is being absorbed by the recitation of "the absorbing dipole". The dipole can be created by unequal distribution of electron by different atoms; thus, it is unclear how the disulfide bridge can have dipole moment.

(b) Claim 103 recites the limitation "the frequency of occurrence" which is "at least 1 fold greater relative to the frequency of occurrence in proteins in general". The frequency of occurrence in proteins in general is not defined by the instant specification and unclear how frequent occurrence of Asn, Gly, His (for example) within an 8Å radius of the indole ring of the aromatic amino acid residue is the frequency in proteins in general. The frequency in protein in general is relative depending on which protein is considered as a protein in general. The term "the frequency of occurrence in protein in general" in claim 103 is a relative term which renders the claim indefinite. The term "the frequency of occurrence in protein in general" is not defined by the claim, the specification does not provide

a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 88-91 and 93-112 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method of covalently attaching the cutinase isolated from *Fusarium solani pisi*, for example, to a carrier comprising: irradiating the protein with 296 nm which resulting in a free thiol group from the disulfide bridge in the presence of tryptophan (Trp) which must reside in a spatial neighbor close enough to be quenched by the disulfide bond (wherein the spatial arrangement is described as a "Trp/Cys-Cys triad" in the instant application, for example); wherein the Trp is excited by 296 nm, wherein quenching breaks disulfide bond and forming free thiol that can be covalently attach to the insoluble support having the functional group forming a covalent bond with free thiol of the protein or peptide; **does not** reasonably provide enablement for a method comprising irradiating at any wave length light to any protein or any peptide comprising one or more aromatic amino acid residue within 10 angstrom of a disulfide bridge to create a thiol group in the protein or the peptide by disulfide bridge disruption; and incubating the irradiated protein or peptide with a thiol to couple to a insoluble support.

The rejection was stated in the previous office action as it applied to previous Claims 31-50 and 88-92. In response to this rejection, applicants have cancelled Claims 1-87 and 92; amended Claims 88-90; and added new Claims 93-112; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that applying standards of enabling disclosure, the claims as amended could be practiced without undue experimentation because the instant specification provide guidance and working examples for claimed method; wherein the specification discloses that disulfide bridges located in close proximity to aromatic amino acids are the most vulnerable to UV-induced disruption and the presence of Trp as a close spatial neighbor in a protein occurs frequently in nature. Applicants further argue that instant specification provides guidance and working examples of UV-induced disruption and that the presence of a disulfide bridge with an aromatic residue such as Trp as a close spatial neighbor in a protein which occurs frequently in nature, and it is a wide spread phenomenon and in view of disclosed many proteins as examples (e.g., cutinase, hen egg white lysozyme, Rhizopus niveus triglyceride lipase, human plasminogen, human placental alkaline phosphatase, chymosin B, and immunoglobulin IgG); thus, one skilled in the art would reasonably expect that irradiating a protein or peptide comprising one or more aromatic amino acid residue within 10 angstrom of a disulfide bridge with a light would create a thiol group in the protein or peptide by disulfide bridge disruption, and instant rejection should be withdrawn.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The Examiner acknowledges that the scope of

enablement is satisfied as long as instant application provides reasonable disclosure for making and using the entire scope claimed invention. The Examiner also acknowledges that the instant amendment clarifying for the limitation of "coupling" (that is the protein or peptide is coupled to the carrier comprising Au or a thiol binding ligand through said created thiol group) satisfies the written description requirement since a thiol binding to a thiol binding ligand is well known in the art. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use of the invention commensurate in scope with these claims for the reasons noted below. The Examiner acknowledge that one skilled in the art can irradiate any protein with any light; however, undue experimentation would be necessary to create an accessible thiol group in any protein; wherein said any protein has to have aromatic amino acid residue(s) within 10 angstrom of a disulfide bridge; so that the thiol group can couple to an insoluble support comprising Au or a thiol-binding ligand through said created thiol group because one skilled in the art would not know which protein has a disulfide bond within 10 angstrom of aromatic amino acid residue(s) and would not know which protein would have aromatic amino acid residue(s) within 10 angstrom of a disulfide bridge so that reduced disulfide bond creating an accessible thiol group which can be used for coupling with the insoluble support; and undue experimentation would be necessary when irradiating with any wavelength to create a thiol from said any protein or polypeptide.

As previously noted, the nature of the invention is drawn to a method of covalently attaching the cutinase isolated from *Fusarium solani pisi* to a carrier

comprising: irradiating the protein with 296 nm which resulting in a free thiol group from the disulfide bridge in the presence of tryptophan (Trp) which must reside in a spatial neighbor close enough to be quenched by the disulfide bond (wherein the spatial arrangement is described as a "Trp/Cys-Cys triad" in the instant application, for example); wherein the Trp is excited by 296 nm, wherein quenching breaks disulfide bond and forming free thiol that can be covalently attach to the insoluble support having the functional group forming a covalent bond with free thiol of the protein or peptide. However, the breadth of instant claims includes a method comprising steps involved with any protein or any peptide having aromatic amino acid residue(s) within 10 angstrom of a disulfide bridge to create a reduced free thiol group in the protein or peptide by disulfide bridge disruption; and incubating the irradiated protein or peptide with said insoluble support comprising Au or a thiol-binding ligand. Applicants teach a method of covalently forming a disulfide bond with a support having a thiol reactive functional group with certain proteins by irradiating 295 nm (i.e., the proteins used in the instant example cutinase, glucose oxidase, two Fab fragment, lysozyme, chimosin, wherein three-dimensional structure of all proteins were known). Prombers et al. (FEBS Lett. 1999 Aug 13; volume 456(3): pages 409-416, as cited in the IDS) teaches one species of protein encompassed within claimed genus method; wherein the disulfide bond in the protein is cleaved by UV irradiation. However, applicants and prior art disclose no direction or guidance on how to make and use the entire scope of claimed method; that is a method of coupling any disulfide bridge containing protein or peptide within 10 angstrom of aromatic amino acid(s) to said insoluble support described in

claims by irradiating and incubating the irradiated protein or polypeptide with the insoluble support having Au or thiol-binding ligand. Furthermore, the disulfide bridge in a protein or polypeptide have to be on the surface of the protein or polypeptide and have tryptophan close by as shown in the structure of the cutinase (see Figure 2 of Prompers et al. (1999) as cited in the IDS). Thus, the specification and prior art fail to describe how to make and use the full scope of claimed genus method sufficiently. Permyakov et al. (2003) disclose that "transfer of electrons to the S-S bonds, resulting in their reduction" (see Abstract); and also disclose the Trp60 which is 6.5 angstrom away from the disulfide bond does not suffer from the UV illumination and concluded that "that the electron transfer from excited tryptophan residues to disulfide bonds depends not only on distance between donor and acceptor, but also on some other factors" (see bottom of right column, page 502). Thus, it is unpredictable for the breadth of the scope (see above) to be used in the method of coupling any disulfide bridge containing protein or peptide to a carrier with Au or a thiol-binding ligand even if the aromatic residues are within the 10 angstroms of a disulfide bond within a protein for one skilled in the art to make and use the entire scope of the method in claims. The said unpredictability makes the relative skill required in the art very high. For all of the above reason, it would require undue experimentation necessary for genus method as encompassed by the breadth of claims as described above.

Withdrawn-Claim Rejections - 35 USC § 102

16. Claims 31-49 and 88-92 are rejected under 35 U.S.C. 102(b) as being anticipated by Prombers et al. (FEBS Lett. 1999 Aug 13; volume 456(3): pages 409-416, as cited in the IDS) is withdrawn by virtue of Applicants' amendment (i.e., adding limitation of "carrier comprising Au or a thiol-binding ligand" in Claim 88).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 88, 91, 93-99, 105-110 and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nisnevitch et al. (J. Biochem. Biophys. Methods, 2001, Volume 49, pages 467-480) in view of Ellison et al. (BioTechniques, 2000, Volume 28, pages 318-320 and 324-326) as evidenced by Stalteri et al (Eur J Nucl Med, 1996, Volume 23, pages 178-87).

Nisnevitch et al. teach general strategies (or a method) for attaching antibody to the solid phase in affinity chromatography. Nisnevitch et al. teach a method of attaching antibody onto a solid-phase-bound activators including a dramatized solid phases which is chemically stable during storage and allow covalent attachment to $-NH_2$, -OH, or -SH groups by gentle mixing with protein" (see page 472, lines 23-26) such as "the case in

the use of hetro-bifunctional agents, like N-succinimidyl 3-(2-pyridyldithio) propionate, which utilize the thiol groups of the Ab" (see page 472, lines 32-34).

Nisnevitch et al. do not teach attaching an antibody with free thiol from the disulfide bind created by irradiating the antibody with UV light.

Ellison et al. teach a method of reducing disulfide bond of monoclonal antibodies for conjugation; wherein the antibody used for the study is PR1A3, a mouse IgG1 monoclonal antibody. The photoreduction procedure by Ellison et al. involves irradiating a vial containing the antibody PR1A3 exposing with UV light (see middle of right column, page 319) that is irradiating at 300 nm as evidenced by the Abstract of Stalteri et al. (reference number 6 in "UV source" middle of left column, page 319); which creates reactive free thiol for labeling monoclonal antibodies. Ellison et al. also teach measurement of "free thiols per antibody produced during irradiation" (see bottom of left column, page 320) and conjugation with a thiol reactive probes comprising biotinylation which binds to alkaline-phosphatase conjugated avidin to show bands in SDS-PAGE (see Figure 4 on page 322).

Ellison et al. do not teach that antibody (Ab) PR1A3 has aromatic amino acid residue(s) within 10Å of the reduced disulfide bridge. Since, the disulfide bond of Ellison et al. were reduced by UV irradiation to produce free thiol for labeling, there would be an aromatic residues within 10Å, otherwise the irradiation would not have created a free thiol by irradiation. Thus, the method step of Ellison et al. meets the limitation of Claims **88(in part), 94-99 and 112**. The focal points of irradiation by Ellison et al. can be said to be focused around the point of disulfide bond(s) by a determination

of the focal points by one skilled in the art; which meets the limitation of Claim 89. Ellison et al. teach the UV radiation generated to a maximum of an average of 14 thiols per immunoglobulin molecule from a theoretical total of 34. If the conjugation is done by a method that creates a disulfide bond, then the created bond can be disrupted by the same method (Claim **110)**.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to attach the antibody PR1A3 (which is irradiated with UV, that is a photo reduction, to create a free sulfide group) onto a solid phase for affinity chromatography bound with a hetero-bifunctional agents like N-succinimidyl 3-(2-pyridyldithio) propionate (which utilizes the free thiol groups of the Ab forming disulfide bond) with a reasonable expectation of success for conjugating the Ab to an solid phase affinity resin. Nisnevitch et al. who teach immobilization of antibodies (Ab) to a solid support was first reported in 1967 [1] and the technology has since found widespread application in affinity chromatography and other area. The motivation for attaching the antibody generated by a method of Ellison et al. to the affinity resin of Nisnevitch et al. is provided by Ellison et al. who teaches the photo reduction of disulfide bond to create free reactive thiol is more advantageous compared to other reduction method to create reactive thiol; wherein the other method is "inconvenient, multistep, time- and material-consuming process" (see bottom of middle column, page 318). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art. Unlike an adsorption process of protein into a solid support which occurs in a random places of solid support, the antibody of Ellison et al. is

attached to the point of "polymers carrying active groups" within the "derivatized solid phase" through a -SH, for example, (see page 472, lines 23-26). Thus, the specific attachment of antibody onto the specific point of active groups in solid phase above would meet the limitation of immobilization is spatially controlled in Claim 106.

Conclusion

17. Claims 88-91 and 93-112 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
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